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Health and Environmental Effects Profile for Chlorobenzilate

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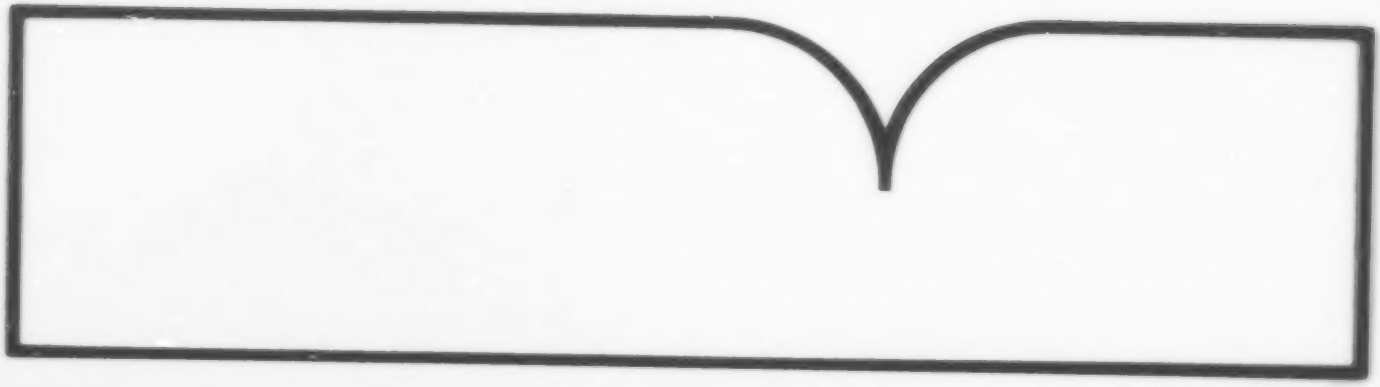

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLOROBENZILATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

The Health and Environmental Effects Profile for chlorobenzilate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chlorobenzilate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for chlorobenzilate is 1.7×10^{-1} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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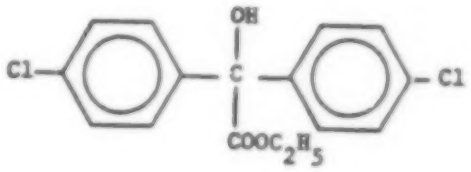
LIST OF ABBREVIATIONS

EC_{50}	Median effective concentration
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chlorobenzilate is the common name for ethyl 4,4'-dichlorobenzilate or ethyl 4-chloro-alpha-(4-chlorophenyl)-alpha-hydroxybenzeneacetate (BCPC, 1977). This acricide was introduced in 1952 by T.R. Geigy S.A. under the trade names of "Akar" and "Folbex" and code number "623992". The structure of chlorobenzilate is depicted below:



Molecular formula: $C_{16}H_{14}Cl_2O_3$

Molecular weight: 325.2

The Chemical Abstracts Service (CAS) Registry number for this compound is 510-15-6.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chlorobenzilate is a pale yellow solid. The technical product is a brownish liquid of ~90% purity (BCPC, 1977). Some of the physical properties of chlorobenzilate are listed below.

Vapor pressure:	2.2×10^{-6} mm Hg at 20°C (BCPC, 1977)
Boiling point:	141-142°C (0.06 mm Hg) (Hawley, 1977)
Solubility:	soluble in most organic solvents; "slightly soluble" in water (BCPC, 1977; Horn et al., 1955)
Hydrolyzed by:	Alkali and strong acids (BCPC, 1977)

1.3. PRODUCTION DATA

Chlorobenzilate is produced by Ciba-Geigy Corporation in McIntosh, AL (SRI, 1983), Arsynco Inc., Bergen, NJ, and Consolidated Chemical Company, Matagordat, TX (U.S. EPA, 1980). Recent production data for the United States are unavailable; however, production in 1977 for Consolidated Chemical Company was reported as 100,000-1,000,000 pounds (U.S. EPA, 1980), and an earlier study estimated that in 1971 production was 2 million pounds (Ouellette and King, 1977).

1.4. USE DATA

Chlorobenzilate is a non-systemic acaricide (miticide). It is recommended for use against phytophagus mites on citrus and deciduous fruit trees (BCPC, 1977). According to the Federal Register (43 FR 29827), 72% of the chlorobenzilate consumed is used on citrus crops in Florida, and the remaining 28% is used in Texas, Arizona and California.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Chlorobenzilate may enter the environment during spray application of the insecticide on citrus crops or during the manufacturing of the compound. Its fate and transport in soil, water or air have not been well studied, though the primary reactions that chlorobenzilate is likely to undergo may include hydrolysis, decarboxylation and photolysis.

Chlorobenzilate may enter the soil directly during application onto citrus crops. The half-life of chlorobenzilate in two fine sand soils was estimated to be between 1.5 and 5 weeks following application of 0.5-1.0 ppm; removal was probably microbial (Wheeler et al., 1973). Rhodotorula gracilis, a yeast isolated from insecticide-treated soils, metabolized chlorobenzilate to 4,4'-dichlorobenzilic acid and 4,4'-dichlorobenzophenone (Miyazaki et al., 1969, 1970; Tu and Miles, 1976; Menzie, 1972). The probable degradation pathway involved the hydrolysis of chlorobenzilate to 4,4'-dichlorobenzilic acid followed by decarboxylation and dehydrogenation of the acids to 4,4'-dichlorobenzophenone (Miyazaki et al., 1970). Complete degradation of the compound did not occur during the 8-week incubation period. This could have been due to the storage of the apolar compound in the fat of the yeast cells, where little enzymatic degradation would take place (Miyazaki et al., 1970).

Mansell et al. (1977) investigated the leachability of chlorobenzilate when applied at a rate of 1.4 kg/ha directly to citrus trees growing in one of three Florida flatwood management treatment areas. These included shallow-tilled (plowed to 15 cm), deep-tilled and soil mixed to 105 cm, and deep-tilled to 105 cm and 56 metric tons/ha of dolomitic limestone mixed with the soil. As would be predicted from the virtual insolubility of

chlorobenzilate in water, there was essentially no leaching of chlorobenzilate. At 5 days after application, chlorobenzilate was not detected in samples of subsurface drainage or surface runoff waters associated with the three soil management treatments.

Chlorobenzilate may enter the water directly through spray drift during application to crops or from erosion or runoff from the soil. Ware et al. (1980) demonstrated that in distilled water (pH 8.0), chlorobenzilate could photodegrade to p,p'-dichlorobenzophenone, p-chlorobenzaldehyde as well as unidentified polar and neutral products when irradiated with UV light for 24-137 hours in a sunlight-simulating photoreactor; a half-life of <1 day was reported. Chlorobenzilate can undergo hydrolysis in the presence of alkali or strong acids (BCPC, 1977); however, information regarding the significance of these reactions in the natural environment was not located.

Although specific data regarding microbial degradation of chlorobenzilate in water were not located in the available literature (see Appendix), data provided by Miyazaki et al. (1970) for soil suggest that degradation by microorganisms may also occur in water.

3. EXPOSURE

STORET contained monitoring data for 260 stations for chlorobenzilate in water. The overall analysis for chlorobenzilate in whole water ranged from undetectable to 66.0 µg/ℓ, with a mean of 0.44 µg/ℓ (n=323); in mud (dry weight) concentrations ranged from 17.0-530.0 µg/kg with a mean of 39.16 µg/kg (n=63); and in sediment, concentrations of chlorobenzilate ranged from 80.0-200 µg/kg with a mean of 126.67 µg/kg (n=3).

Following application of 9.5 ppm, residues of chlorobenzilate persisted in and on the rinds of lemons for >160 days. Average applications of 15 ppm chlorobenzilate on oranges and lemons resulted in a persistence half-life of ~66 days (Jeppson and Gunther, 1970).

The U.S. EPA's (1978) estimates of human dietary exposure to chlorobenzilate are based on residue data and the extent to which the acaricide is used on each of the food crops for which it is registered. The maximum residue present in citrus crops and nuts is estimated to be 0.1 ppm; in other fruit (e.g., apples and pears) it is estimated to be 5 ppm; in beef and lamb, 0.04 ppm; and in milk, 0.002-0.04 ppm (EPA, 1978). The average human exposure to chlorobenzilate from the United States diet has been estimated to be <4.6 µg/day for the general population and <5.6 to <12.5 µg/day for the Florida population (44 FR 9555).

Data regarding the actual amounts of chlorobenzilate exposure to ground applicators and citrus pickers were unavailable; however, data on exposure of workers during application of other pesticides (Wolfe et al., 1967) were used to estimate these amounts at 120-140 mg/day dermally and 1 mg/day by inhalation (U.S. EPA, 1978). Since similar pesticides are known to be absorbed through the skin at a rate of 10%, and pesticides that are inhaled are assumed to be absorbed 100% (Feldman and Maibach, 1974), the daily dermal dose range was estimated to be 12-40 mg and the inhalation dose, 1 mg (U.S. EPA, 1978).

4. PHARMACOKINETICS

4.1. ABSORPTION

Specific data regarding the absorption of chlorobenzilate were not located in the available literature; however, it can be inferred from distribution and excretion data in rats and dogs (Horn et al., 1955) that chlorobenzilate is absorbed from the gastrointestinal tract of both species following oral administration (Sections 4.2. and 4.4.).

4.2. DISTRIBUTION

At the termination of oral administration of 12.8 mg/kg/day chlorobenzilate to male and female mongrel dogs 5 days/week for 35 weeks, chlorobenzilate was found primarily in the blood (8.5 and 9.4 ppm), the kidney (1.3 and 12.5 ppm) and the liver (3.2 and 22.5 ppm). An oral dose of 64.1 mg/kg /day chlorobenzene to dogs for 35 weeks also produced higher levels of compound in the blood (17.3 and 31.6 ppm), liver (23.6 ppm) and kidney (12.6 and 29.4 ppm) than in other tissues. Low levels of the compound were detected in the brain, fat and muscle (Horn et al., 1955). In the same study, Horn et al. (1955) fed 500 ppm chlorobenzilate to rats for 17 weeks and 800 ppm for 44 weeks, and at termination of the study, found the compound primarily in the liver (25.1 ppm and 14.7-25.1 ppm, respectively) and kidney (no data for 500 ppm; 9.4-27.0 ppm for 800 ppm). Chlorobenzilate was also detected in lesser amounts in the brain, fat and muscle. Although the blood was not analyzed in the rats, the authors stated that the quantity of chlorobenzilate found in the livers of both animals could be attributed to the larger quantity of blood present in this organ. The Schechter-Haller reaction, which tests for the 4,4'-dichlorodiphenyl methyl group (Horn et al., 1955), was used to quantitate chlorobenzilate. Hence, the values given above may refer to metabolites (such as dichlorobenzilic acid) as well as to the parent compound.

4.3. METABOLISM

Several studies were located which suggest that chlorobenzilate is metabolized by mammalian systems to yield 4,4'-dichlorobenzophenone and p'-chlorobenzilic acid.

Knowles and Ahmad (1971) incubated ^{14}C-chlorobenzilate (labeled at both aliphatic carbon atoms of the benzilic acid moiety) with rat liver fractions and NADPH for 4 hours. Chlorobenzilate was metabolized by all liver fractions (nuclear, nuclear supernatant, mitochondrial, microsomal and soluble). Maximum activity was associated with the nuclear supernatant (i.e., supernatant resulting from sedimentation of nuclei at 600 xg), and the microsomal fraction, each of which metabolized ~75% of the added compound. The major degradation products were identified as 4,4'-dichlorobenzophenone and p'-chlorobenzoic acid. Exclusion of NADPH from the soluble and microsomal incubation mixtures appeared to have little effect on the disappearance of chlorobenzilate; however, it did enhance the accumulation of 4,4'-dichlorobenzoic acid, suggesting that it was partially degraded by oxidative enzymes (Knowles and Ahmad, 1971). In the same study, the authors incubated a larger amount (10 mg) of unlabeled chlorobenzilate with rat liver microsomes and NADPH for 4 hours in order to identify the degradation pathway. The results indicated that chlorobenzilate is hydrolyzed at the ester linkage, yielding 4,4'-dichlorobenzilic acid. This compound is subsequently decarboxylated to 4,4'-dichlorobenzhydrol, which is dehydrogenated to 4,4'-dichlorobenzophenone and further converted to p'-chlorobenzoic acid (Knowles and Ahmad, 1971).

In an abstract of a study by Brady et al. (1982), p,p'-dichlorobenzoic acid, p,p'-dichlorobenzhydrol and p,p'-dichlorobenzophenone were identified as urinary metabolites after rats were dosed with chlorobenzilate by gavage (0.1, 0.01 and 0.001 of the LD_{50}), or treated dermally with 1 g/kg.

Levy et al. (1981) measured an overall average value of 1.3 ppm p,p'-chlorobenzophenone in the urine of male citrus-grove field workers exposed to 3.8 kg/ha chlorobenzilate 10 hours/day for 23 days.

4.4. EXCRETION

Chlorobenzilate metabolites appear to be excreted fairly rapidly in the urine following oral administration of the compound to dogs. Horn et al. (1955) orally administered 12.8 or 64.1 mg/kg/day to male and female mongrel dogs for 5 days. Urine and feces were analyzed for chlorobenzilate and metabolites by the Schechter-Haller reaction (see Section 4.3.) every 24 hours for 10 days, starting with the day the first dose was administered. For the animals at the low dose level, ~42.7 and 41.8% of the total administered doses (461.5 and 391.0 mg, respectively) were excreted in the urine and 4.3 and 7.5% were excreted in the feces within 10 days. At the higher dose level, ~21.8 and 15.1% of the total administered doses (2755.5 and 3108.0 mg, respectively) were excreted in the urine and 6.6% was excreted in the feces within 10 days. For both dose levels, excretion of chlorobenzilate (metabolite) could no longer be detected at 3-4 days after the last dose. The identity of the excreted compound was not established. but the ester linkage was no longer present, the 4,4'-dichlorophenyl methyl moiety was still present, and the authors concluded that the excreted compound may have been 4,4'-dichlorobenzoic acid.

5. EFFECTS

5.1. CARCINOGENICITY

NCI (1978) tested the oncogenicity of chlorobenzilate in Osborne-Mendel rats and B6C3F1 mice (Table 5-1). In rats, the incidence of cortical adenoma of the adrenal gland was statistically significantly elevated, relative to control values, in low dose males and high dose females (see Table 5-1). In addition, results of the Cochran-Armitage test for dose-related trend indicated a positive association between dosage and the incidence of this tumor in females. There appeared to be a slight (but not statistically significant) increase in the incidence of malignant lymphomas among treated rats, and a negative association between treatment and the incidence of hemangiosarcoma. In mice, the incidences of hepatocellular carcinoma were statistically significantly elevated in all treated groups when compared with controls. The NCI (1978) noted a possible negative association between treatment and the incidence of malignant lymphomas in female mice. The NCI concluded that these results provide sufficient evidence for the carcinogenicity of chlorobenzilate in B6C3F1 mice but not in Osborne-Mendel rats (NCI, 1978).

Bionetics Research Laboratories (BRL, 1968) and Innes et al. (1969) tested the tumorigenicity of chlorobenzilate by oral administration to two hybrid strains [(C57BL/6 x C3H/AnF)F_1 and (C57BL/6 x AKR)F_1] of mice for 83 weeks. Male mice of both strains had statistically significant increases in hepatomas compared with their respective control groups (Table 5-2). Results of this study indicate that chlorobenzilate is carcinogenic for the liver of male mice of two strains.

Horn et al. (1955), in a 2-year study using 0, 50 and 500 ppm chlorobenzilate in the diet of rats, observed tumors in some of the animals

TABLE 5-1

Summary of Oral Carcinogenicity of NCI (1978) Study

Species/ Strain	Sex	Dose or Exposure* (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Rats/ Osborne-Mendel	M F	2995 2229	78 78	110 111	technical grade	diet	hemato-poietic system	malignant lymphoma	2/50 3/50
Rats/ Osborne-Mendel	M F	1600 1175	78 78	110 111	technical grade	diet	hemato-poietic system	malignant lymphoma	5/50 0/49
Rats/ Osborne-Mendel	M F	0 0	NA NA	111 111	technical grade	diet	hemato-poietic system	malignant lymphoma	1/49 1/50
Rats/ Osborne-Mendel	M F	2995 2229	78 78	110 111	technical grade	diet	circulatory system	hemangio-sarcoma	1/50 0/50
Rats/ Osborne-Mendel	M F	1600 1175	78 78	110 111	technical grade	diet	circulatory system	hemangio-sarcoma	4/50 1/49
Rats/ Osborne-Mendel	M F	0 0	NA NA	111 111	technical grade	diet	circulatory system	hemangio-sarcoma	12/49 4/50
Rats/ Osborne-Mendel	M F	2995 2229	78 78	110 111	technical grade	diet	adrenal	cortical adenoma	3/49 5/47 (P=0.024)
Rats/ Osborne-Mendel	M F	1600 1175	78 78	110 111	technical grade	diet	adrenal	cortical adenoma	6/49 (P=0.049) 2/47
Rats/ Osborne-Mendel	M F	0 0	NA NA	111 111	technical grade	diet	adrenal	cortical adenoma	0/46 0/50

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose or Exposure* (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Rats/ Osborne-Mendel	F F F	2229 1175 0	78 78 NA	111 111 111	technical grade	diet	thyroid	C-cell adenoma or C-cell carcinoma	2/47 3/47 5/50
Rats/ Osborne-Mendel	F F F	2229 1175 0	78 78 NA	111 111 111	technical grade	diet	mammary gland	fibro-adenoma	16/50 14/49 15/50
Rats/ Osborne-Mendel	F F F	2229 1175 0	78 78 NA	111 111 111	technical grade	diet	uterus	endometrial stromal polyp	4/46 1/47 4/49
Mice/ B6C3F1	M F	7846 5908	78 78	90 91	technical grade	diet	liver	hepato-cellular carcinoma	22/45 (P=0.034) 13/50 (P=0.007)
	M F	4231 3200	78 78	90 91	technical grade	diet	liver	hepato-cellular carcinoma	32/48 (P=0.001) 11/49 (P=0.016)
	M F	0 0	NA NA	90 90	technical grade	diet	liver	hepato-cellular carcinoma	4/19 0/20
Mice/ B6C3F1	M F	7846 5908	78 78	90 91	technical grade	diet	hemato-poietic	malignant lymphoma system	1/48 0/50
	M F	4231 3200	78 78	90 91	technical grade	diet	hemato-poietic	malignant lymphoma system	1/49 1/50
	M F	0 0	NA NA	90 90	technical grade	diet	hemato-poietic	malignant lymphoma system	1/19 3/20

*TWA dietary concentrations

NA = Not applicable

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TABLE 5-2

Summary of Oral Carcinogenicity Study of BRL (1968) and Innes et al. (1969)

Species/ Strain	Sex	Dose or Exposure[a] (ppm)	Duration of Treatment[a] (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State[a]	Target Organ	Tumor Type	Tumor Incidence (P value)
Mice/ (C57BL/6 x C3H/Anf)F_1	M	603	82	82	99.3%	diet	liver stomach	hepatoma papillomas	9/17 3/17
Mice/ (C57BL/6 x C3H/Anf)F_1	F	603	82	82	99.3%	diet	liver stomach	hepatoma papillomas	0/18 6/18
Mice/ (C57BL/6 x C3H/Anf)F_1	M	0.0	NA	82	NA	diet	liver stomach	hepatoma papillomas	8/79[b] 9/79
Mice/ (C57BL/6 x C3H/Anf)F_1	F	0.0	NA	82	NA	diet	liver stomach	hepatoma papillomas	0/87[b] 21/87
Mice/ (C57BL/6 x AKR)F_1	M	603	82	82	99.3%	diet	liver	hepatoma	7/17
Mice/ (C57BL/6 x AKR)F_1	F	603	82	82	99.3%	diet	liver	hepatcma	0/18
Mice/ (C57BL/6 x AKR)F_1	M	0.0	NA	82	NA	diet	liver	hepatoma	5/90[b]
Mice/ (C57BL/6 x AKR)F_1	F	0.0	NA	82	NA	diet	liver	hepatoma	1/82[b]

[a]Treatment was by gavage, at 215 mg/kg chlorobenzilate/kg/day in 0.5% gelatin from day 7-28 of life. The compound was then administered in the diet at 603 ppm for an additional 79 weeks and the survivors were killed at 83 weeks of age.

[b]Total negative control mice necropsied.

NA - Not applicable.

including controls. Too few animals were examined histopathologically for proper statistical analysis and tumor incidences in the control group were often greater than in the experimental groups; therefore, these data are unreliable indicators of carcinogenicity (U.S. EPA, 1978).

The U.S. EPA (1978) has reviewed the results of an unpublished carcinogenicity study performed for the Ciba-Geigy Corporation by Woodard Research Corporation (1976). In this study, rats were fed chlorobenzilate in the diet. Consultants to the U.S. EPA (1978) concluded that the data from the Woodard study "were unreliable for assessing the oncogenicity of chlorobenzilate" because animals that died before the end of the study were not necropsied, and histopathologic examinations were performed on no more than 20% of the animals from each group. Tumor incidences in control groups were often higher than in treated groups. Therefore, these results are not useful for assessing the oncogenicity of chlorobenzilate.

In addition to the chronic feeding study, BRL (1968) performed a screening test in which male and female mice of the (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 strains were administered a single subcutaneous injection of 1000 mg chlorobenzilate/kg and necropsied ~18 months later. No statistically significant increases in tumor incidences were found.

Reuber (1977, 1980) reexamined the histological sections from the oral carcinogenicity studies on mice and rats (i.e., NCI, 1978; Innes et al., 1969) and reported different incidences of tumors (and nonneoplastic lesions) among treated groups than were reported by the original investigators. Because the original evaluations of these studies have been subjected to rigorous review, while Reuber's reevaluations have not, and because Reuber has been censured by the NCI for his reevaluations of pesticide carcinogenicity studies (Pesticide and Toxic Chemical News, 1981), his interpretations will not be considered further in an assessment of the carcinogenicity of this chemical.

IARC (1974) considered the available feeding studies of Innes et al. (1969) and Horn et al. (1955) inadequate for evaluation of the carcinogenic potential of chlorobenzilate, and in 1983 did not list chlorobenzilate as a chemical for which there is sufficient evidence of carcinogenicity in animals (IARC, 1983). It is unclear whether IARC evaluated the NCI (1978) data on chlorobenzilate when compiling the 1982 list.

5.2. MUTAGENICITY

Chlorobenzilate was reported negative in the Ames reversion-assay with Salmonella typhimurium (strains TA100, TA98, TA1535, TA1537, TA1538) and a strain (WP2 her) of Escherichia coli when tested at doses up to 5000 µg/plate, with and without the S-9 metabolic fraction (Moriya et al., 1983). No data were contained in the report.

Fahrig (1974) reported that chlorobenzilate failed to induce mutations in the following in vitro assays with microorganisms:

- Spot test: back mutation in two auxotrophic strains (a 21 and a 742) of Serratia marcescens and forward mutations in a galactose-negative strain (Gal R^S) of E. coli.
- Liquid holding test: forward mutation to streptomycin resistance in E. coli and mitotic gene conversion in Saccharomyces cerevisiae.

Tests were conducted only without activation. Neither concentrations tested nor data were reported.

In an abstract Sobti et al. (1981) stated that chlorobenzilate at 3 µg/ml did not increase sister chromatid exchange (SCE) frequency but did induce chromatid and chromosome structural and numerical aberrations in human lymphoid cells (LAZ-007). In a subsequent paper from the same laboratory (Sobti et al., 1983) chlorobenzilate was reported cytotoxic and caused delayed cell division but again did not induce SCE formation when tested at 10^{-6}, 10^{-5} and 10^{-4} molar concentrations in the same cell line as

before. These concentrations correspond to 0.3, 3 and 30 µg/mℓ. The testing was conducted without activation and chromosome aberrations were not scored in this report.

Negative results were obtained for chlorobenzilate (97% pure) in the mouse sperm morphology assay. The study was performed with strain (C57BL/6 x C3H)F_1 male mice injected intraperitoneally with doses of 0.75, 0.38, 0.19, 0.09 and 0.05 g/kg/day chlorobenzilate in 0.25 mℓ corn oil for 5 consecutive days (Osterloh et al., 1983).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic potential of chlorobenzilate were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

In a 99-day study using 20, 100, 500 or 2500 ppm chlorobenzilate in the diet, spermiogetic injury and atrophy of the testes were found in 25% (5/20) of the rats treated with 2500 ppm chlorobenzilate. A NOEL of 500 ppm was identified for this study (Potrepka, 1978).

In a 3-generation study, F_0 rats were fed 50 ppm and subsequent genera- tions were fed 25 or 50 ppm chlorobenzilate in the diet. A significant decrease in testicular weights was found in F_{1b} males at the 50 ppm dose level

when compared with the controls (Woodard Research Corporation, 1976).

In chronic studies (see Section 5.5.), testicular atrophy has also been observed to occur at higher incidences in rats fed chlorobenzilate in the diet than among rats fed control diet (NCI, 1978; Horn et al., 1955).

5.5. CHRONIC TOXICITY

Some information on toxicity can be obtained from the NCI (1978) carci- nogenicity study. There were significant and dose-related increases in

atrophy of the testes in male Osborne-Mendel rats fed TWA dietary levels of 1600 or 2995 ppm chlorobenzilate for 78 weeks (NCI, 1978). Experimental details were presented in Section 5.1. Testicular atrophy occurred in 53% (26/49) of the rats fed 1600 ppm and 63% (31/49) of the rats fed 2995 ppm chlorobenzilate compared with 20% (9/44) for the controls. No other non-neoplastic histopathologic effects were observed in either sex of rat in the NCI (1978) study, and survival was not affected by treatment. Slight, dose-related depressions in mean body weights occurred during weeks 10-90 in both males and females. The females had received 1175 or 2229 ppm of chlorobenzilate in the diet. B6C3F1 mice fed 4231 or 7846 ppm (males) and 3200 or 5908 ppm (females) of chlorobenzilate in the diet had no adverse effects on survival and no non-neoplastic histopathologic effects (NCI, 1978). Slight, dose-related depression in mean bw was seen in females throughout the study and in males through week 80 of the study.

Horn et al. (1955) found testicular atrophy in 69% (9/13) of male Carworth Farm rats fed 50 ppm and 100% (14/14) fed 500 ppm chlorobenzilate for 2 years compared with 25% (4/16) for the control group. A significant reduction in growth was also observed for the males in the 500 ppm group (Horn et al., 1955). No other histopathologic effects were noted and survival was not affected by treatment. Twenty males and 20 females were tested at the 0 and 500 ppm levels; 20 males and no females were tested at the 50 ppm dose level.

In an unpublished study performed by Hazelton Laboratories (1965), adult purebred beagles (3 males and 3 females/dose group) were fed 0, 100 or 500 ppm chlorobenzilate in the diet for 104 weeks. Another group of dogs were fed 5000 ppm chlorobenzilate for 1-14 weeks and 3000 ppm chlorobenzilate for 20-104 weeks. Effects of chlorobenzilate treatment were summarized

by Reuber (1980), who apparently had access to the report. Dogs ingesting the 5000 ppm dose level of chlorobenzilate had poor appetites, lost weight and developed anemia by the 13th week. There were also increases in serum alkaline phosphatase, lowering of serum protein and reversal of the albumin/globulin ratio. One dog given the 3000 ppm dose level experienced diarrhea, weight loss and anemia by the 56th week. Some dogs from each dose group developed anemia and cardiac changes and dogs in the 5000 ppm dose group had enlarged spleens and livers. Histologic examination revealed extramedullary hematopoiesis of the liver and spleen and erythroid hyperplasia of the bone marrow in the highest dose group (Reuber, 1980).

5.6. OTHER RELEVANT INFORMATION

The acute oral LD_{50}s for rats were reported as 1040 mg/kg for males and 1220 mg/kg for females (Gaines, 1960, 1969). An oral LD_{50} of 700 mg/kg was also reported for the rat (NIOSH, 1983). An oral LD_{50} for the mouse was 729 mg/kg (NIOSH, 1983), and 700 mg/kg for the hamster (NIOSH, 1983; Cabral et al., 1979).

An inhalatory LC_{50} for an unspecified mammal was reported as 500 ppm (NIOSH, 1983), and a dermal LD_{50} for rats was >5000 mg/kg (Gaines, 1960).

Following oral administration of 100-3160 mg/kg to male albino mice and rats, preening and depression were observed at all levels (Horn et al., 1955). There were also signs of lacrimation, salivation, diarrhea and deep, rapid respiration. At the higher dosage levels, many animals had sprawling of the hind limbs and absent righting, placement and pain reflexes, followed by coma and death. At necropsy, animals showed hemorrhagic lungs and irritated intestines (Horn et al., 1955).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The 48-hour static LC_{50} value for chlorobenzilate to rainbow trout, Salmo gairdneri, was 0.710 mg/ℓ (USDI, 1968).

The 48-hour EC_{50} for immobilization of Daphnia pulex was 0.870 mg chlorobenzilate/ℓ (Sanders and Cope, 1966). Immobilization of Daphnia magna within 50 hours required 1.4 mg chlorobenzilate/ℓ (Anderson, 1960). Another common species of cladoceran, Simocephalus serrulatus, was slightly more sensitive than Daphnia sp., having a 48-hour EC_{50} for immobilization of 0.550 mg chlorobenzilate/ℓ (Sanders and Cope, 1966).

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic chlorobenzilate exposure to aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of chlorobenzilate on aquatic plants were not located in the available literature.

6.4. RESIDUES

Pertinent data regarding chlorobenzilate residues in aquatic organisms or the aquatic environment were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Chlorobenzilate was reported to inhibit the activity of Na^+-K^+ ATPase and Mg^{2+} ATPase, in vitro (Cutkomp et al., 1972). The activities of the ATPases, derived from bluegill sunfish brain, were reduced by 19.3 and 18.7%, respectively, at 41.7 mM chlorobenzilate concentration.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Guidelines or standards which suggest allowable exposure concentrations for airborne exposures have not been established.

The U.S. EPA has set tolerances for chlorobenzilate residues in or on certain agricultural commodities as follows: 15 ppm in or on almond hulls; 5 ppm in or on apples, citrus fruits, melons and pears; 0.5 ppm in or on cottonseed and meat, fat and meat byproducts of cattle and sheep; and 0.2 ppm in or on almonds and walnuts (Code of Federal Regulations, 1980).

FAO/WHO (1969) has established a human ADI for chlorobenzilate of 0.02 mg/kg/day or 1.2 mg/day for a 60 kg human. It should be noted that this recommendation was made prior to the availability of the cancer bioassay results. Cancellation of some uses has been recommended based on evidence that chlorobenzilate is a carcinogen in experimental animals and has been shown to have adverse testicular effects (44 FR 9562).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of chlorobenzilate were not located in the available literature.

8. RISK ASSESSMENT

Chlorobenzilate has been found to be carcinogenic in male and female $B6C3F_1$ mice (NCI, 1978) and in male mice of two strains, [(C57Bl/6 x C3H/Anf F_1) and (C57Bl/6 x AKR) F_1] (Innes et al., 1969). The available mutagenicity data on chlorobenzilate are too limited for use in risk assessment.

In a 99-day study, 2500 ppm of chlorobenzilate caused spermiogenetic injury and atrophic testes in rats (Potrepka, 1978) and in a 3-generation study, F_{1b} rats fed 50 ppm had decreased testicular weights (Woodard Research Corporation, 1976).

There were significant increases in the incidences of testicular atrophy in rats fed 1600 or 2995 ppm chlorobenzilate for 78 weeks (NCI, 1978), and in rats fed 50 or 500 ppm for 2 years (Horn et al., 1955). Dogs fed 3000 and 5000 ppm chlorobenzilate experienced cardiac changes, extramedullary hematopoiesis of the liver and spleen and hyperplasia of the bone marrow (Reuber, 1980).

Although the evidence for chlorobenzilate carcinogenicity is limited to one species, the U.S. EPA has recommended cancelling all non-citrus uses of chlorobenzilate because, as stated in the Federal Register (44 FR 9562), the compound "poses a risk of cancer and adverse testicular effects to humans." The Agency has proposed continued registration of chlorobenzilate use on citrus crops in Florida, Texas, California and Arizona, but is requiring a 3-generation reproductive study to evaluate further the risks associated with use on citrus crops (44 FR 9562).

The data regarding liver tumors in mice from the carcinogenicity studies by the NCI (1978) and by BRL (1968) can be used to derive a carcinogenic potency factor (q_1^*) for humans; the data from the BRL (1968) study yields the highest human q_1^*. Assuming that a mouse consumes the equivalent of 13% of its body weight/day as food, the dose for the dietary portion of the BRL (1968) study is 78.4 mg/kg/day. The TWA dose for the entire study period (dietary and gavage) was then calculated to be 83.4 mg/kg/day. Based on the hepatoma response of male mice [strain (C57Bl/6 x C3H/Anf) F_1] of 9/17 for treated mice versus 8/79 for the controls, and using the linearized multistage model adopted by the U.S. EPA (45 FR 79318), a carcinogenic potency factor (q_1^*) of 1.66×10^{-1} $(mg/kg/day)^{-1}$ can be derived for humans. The conversion factor used in the calculation of q_1^* values for humans (assuming 70 kg body weight) from animal data was the cube root of the body weight ratio (45 FR 79318). The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 6.02×10^{-5} mg/kg/day, or 4.21×10^{-3} mg/day for a 70 kg man. The hepatoma response of strain (C57Bl/6 x AKR) F_1 male mice gives a similar but slightly lower value for the q_1^* (see Appendices B and C for the derivation of q_1^*).

Doses can be calculated from the dietary levels in the NCI (1978) study in a similar manner: dietary levels of 4231 and 7846 ppm chlorobenzilate correspond to doses of 550 and 1020 mg/kg/day for male mice and dietary levels of 3200 and 5908 ppm correspond to doses of 416 and 768 mg/kg/day for female mice. A q_1^* of 5.51×10^{-2} $(mg/kg/day)^{-1}$ was derived for humans based on the hepatocellular carcinoma response of the males. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 1.81×10^{-4} mg/kg/day or 1.20×10^{-2} mg/day for a 70 kg man. The response

at the high dose was dropped because of a poor fit to the linearized multistage model. The human q_1^* based on the hepatocellular carcinoma response of the female mice was similar to but slightly lower than the human q_1^* based on the data from the males. (See Appendices D and E for details.)

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies of chlorobenzilate, but the data do not necessitate a change in the risk assessment.

9. REFERENCES

Anderson, B.G. 1960. The toxicity of organic insecticides to Daphnia. In: C.M. Tarzwell (comp.), Biological Problems in Water Pollution Trans. 1959 Seminar. Cincinnati, Ohio. Robt. A. Taft San. Eng. Center Tech. Rept. W60-3, p. 94-95. (Cited in Battelle's Columbus Laboratories, 1971)

Bartsch, E., D. Eberle, K. Ramsteiner, A. Tomann and M. Spindler. 1971. The carbinole acaricides: Chlorobenzilate and chloropropylate. Residue Rev. 39: 1-88.

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Vol. 3. Effects of Chemicals on Aquatic Life. U.S. EPA, Washington, DC. Water Pollut. Contr. Res. Ser. 18050GWV05/71.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed. 594 p.

Brady, S.S., K.A. Levy, H.F. Enos, R.C. Duncan and C.D. Pfaffenberger. 1982. Development of methodology for determining human exposure to chlorobenzilate. ACS Symp. Ser. ISS Pestic. Residues Exposure. 182: 105-118.

BRL (Bionetics Research Laboratories). 1968. Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected and Industrial Chemicals. I. Carcinogenic Study. Prepared for National Cancer Institute Report No. NCI DCCP-C6 1973-1-1. NTIS PB-223-157.

Cabral, J.R.P., F. Raitano, T. Mollner, S. Broncayk and P. Shubik. 1979. Acute toxicity of pesticides in hamsters. Toxicol. Appl. Pharmacol. 48(1): A192.

Code of Federal Regulations. 1980. Ethyl 4,4-dichlorobenzilate. Tolerances for residues. 67 CFR 301.09.

Cutkomp, L.K., D. Desaiah and R.B. Koch. 1972. In vitro sensitivity of fish brain ATPases to organochlorine acaricides. Life Sci. 11(23): 1123-1233.

Fahrig, R. 1974. Comparative mutagenicity with pesticides. IARC Sci. Publ. 10: 161-181.

FAO/WHO (Food and Agriculture Organization/World Health Organization). 1969. Pesticide Residues in Food. Report of the 1968 joint meeting of the FAO working party of experts on pesticide residues and the WHO expert committee on pesticide residues. FAO Agric. Studies No. 78; WHO Tech. Report Ser. No. 417. (Cited in Bartsch et al., 1971)

Feldman, R.J. and E.I. Maibach. 1974. Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28: 126-132.

Gaines, T.B. 1960. The acute toxicity of pesticides to rats. Toxicol. Appl. Pharmacol. 2: 88-99.

Gaines, T.B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14(3): 515-534.

Hawley, G.G., Ed. 1977. The Condensed Chemical Dictionary. Ninth edition. Van Nostrand Reinhold Company, NY. p. 194.

Hazelton Laboratories. 1965. Two-year Dietary Feeding Study - Purebred Beagles; Chlorobenzilate, Final Report, Hazelton Laboratories. Unpublished study. (Cited in Reuber, 1980)

Horn, H.J., R.B. Bruce and O.E. Paynter. 1955. Toxicology of chlorobenzilate. J. Agric. Food Chem. 3(9): 752-756.

IARC (International Agency for Research on Cancer). 1974. In: Some Organochlorine Pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Lyon, France: IARC, WHO, Vol. 5, p. 75.

IARC (International Agency for Research on Cancer). 1983. In: Miscellaneous Pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon, France: WHO. IARC, Vol. 30, p. 73.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Jeppson, L.R. and F.A. Gunther. 1970. Acaricide residues on citrus foliage and fruits and their biological significance. Residue Rev. 33: 101-136.

Knowles, C.O. and S. Ahmad. 1971. Comparative metabolism of chlorobenzilate, chloropropylate, and bromopropylate acaricides by rat hepatic enzymes. Can. J. Physiol. Pharmacol. 49(6): 590-597.

Levy, K.A., S.S. Brady and C.D. Pfaffenberger. 1981. Chlorobenzilate residues in citrus worker urine. Bull. Environ. Contam. Toxicol. 27(2): 235-238.

Mansell, R.S., D.V. Calvert, E.H. Stewart, et al. 1977. Fertilizer and pesticide movement from citrus groves in Florida flatwood soils. Prepared for U.S. EPA, Environmental Research Laboratory, Athens, GA. EPA 600/2-77-177. NTIS PB 272-889.

Menzie, C.M. 1972. Fate of Pesticides in the Environment. Ann. Rev. Entomol. 17: 199.

Miyazaki, S., G.M. Boush and F. Matsumura. 1969. Metabolism of ^{14}C-chlorobenzilate and ^{14}C-chloropropylate by Rhodotorula gracilis. Appl. Microbiol. 18(6): 972-976.

Miyazaki, S., G.M. Boush and F. Matsumura. 1970. Microbial degradation of chlorobenzilate (ethyl 4,4'-dichlorobenzilate) and chloropropylate (isopropyl 4,4'-dichlorobenzilate). J. Agric. Food Chem. 18(1): 87-91.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay ssytem. Mutat. Res. 116(3-4): 185-216.

NCI (National Cancer Institute). 1978. Bioassay of chlorobenzilate for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Sci. No. 75. DHEW/PUB/NIH-78-1325. PB-287123. 89 p.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). May, 1983. Online.

Osterloh, J., G. Letz, S. Pond and C. Becker. 1983. An assessment of the potential testicular toxicity of 10 pesticides using the mouse-sperm morphology assay. Mutat. Res. 116(3-4): 407-415.

Ouellette, R.P. and T.A. King. 1977. Chemical Week Pesticides Register. McGraw-Hill Book Company, NY. p. 160.

Pesticide and Toxic Chemicals News. 1981. Dr. Mel Reuber, pathologist, gets sharp censure, warning from his supervisor. 9(21): 22-23.

Potrepka, R.F. (CED). 1978. EPA memo of June 5, 1978 to T.B. Boyd (SPRD). Testicular atrophy in rats from chlorobenzilate. Position Document 3, U.S. EPA, Arlington, VA. (Cited in U.S. EPA, 1978)

Reuber, M.D. 1977. Carcinomas of the liver and forestomach in mice ingesting chlorobenzilate. Digestion. 16: 308-316.

Reuber, M.D. 1980. Carcinogenicity of chlorobenzilate in mice, rats, and dogs. Clin. Toxicol. 16(1): 67-98.

Sanders, H.O. and O.B. Cope. 1966. Toxicities of several pesticides to two species of cladocerans. Trans. Am. Fish Soc. 95(2): 165-169.

Sobti, R.C., A. Krishan, C. Pfaffenberger, P.W.A. Mansell and J. Davies. 1981. Cytogenetic monitoring of environmental pollutants in south Florida, USA. Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol. 22(0): 110.

Sobti, R.C., A. Krishan and J. Davies. 1983. Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells in vitro. II. Organochlorine pesticides. Arch. Toxicol. 52(3): 221-231.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. SRI International, Menlo Park, CA.

Tu, C.M. and J.R.W. Miles. 1976. Interactions between insecticides and soil microbes. Residue Rev. 64: 17-65.

USDI (United States Department of the Interior). 1968. Water Quality Criteria: Report of the National Technical Advisory Committee to the Secretary of the Interior. Fed. Water Pollut. Contr. Admin., Washington, DC.

U.S. EPA. 1978. Chlorobenzilate: Position Document 3. Prepared by J.B. Boyd, Special Pesticide Review Division, U.S. EPA, Arlington, VA, for U.S. EPA, Washington, DC. NTIS PB 80-21-3887. 123 p.

U.S. EPA. 1980. 1977 TSCA Plant and Production file. On tape.

Ware, G.W., D.G. Crosby and J.W. Giles. 1980. Photodecomposition of DDA. Arch. Environ. Toxicol. 9(2): 135-146.

Wheeler, W.B., D.F. Rothwell and D.H. Hubbell. 1973. Persistence and microbial effects of Acrol and chlorobenzilate to two Florida soils. J. Environ. Qual. 2(1): 115-118.

Wolfe, H.R., W.F. Durham and J.F. Armstrong. 1967. Exposure of workers to pesticides. Arch. Environ. Health. 14: 622-633. (Cited in U.S. EPA, 1978)

Woodard Research Corporation. 1976. Chlorobenzilate Safety Evaluation by Dietary Feeding to Rats for 104 Weeks: Final Report. (Unpublished). Geigy Chemical Corporation, Yonkers, NY. Confidential. (Cited in U.S. EPA, 1978 and Reuber, 1980)

APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6, 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment. Cincinnati, OH. 94 p.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. 593 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1983. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. SRI, Menlu Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1982. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call In Program. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1983. CHIB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1982. Synthetic Organic Chemicals. U.S. Production and Sales, 1981. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: Chlorobenzilate

Reference: BRL, 1968; Innes et al., 1969

Species, Strain, Sex: mice, (C57BL/6 x C3H/Anf)F_1, male

Body Weight: 0.36 kg (measured)

Length of Exposure (l_e) = 574 days

Length of Experiment (L_e) = 574 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: liver/hepatoma

Route, Vehicle: oral, by gavage in 0.5% gelatin for 21 days, then in diet for 553 days.

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	8/79
215 mg/kg/day x 21 days, 603 ppm in diet x 553 days	83.4	9/17

Human $q_1^* = 1.66 \times 10^{-1}$ (mg/kg/day)$^{-1}$

10^{-5} risk level = 6.02×10^{-5} mg/kg/day = 4.21×10^{-3} mg/day for 70 kg man

APPENDIX C

Cancer Data Sheet for Derivation of q_1^*

Compound: Chlorobenzilate

Reference: BRL, 1968; Innes et al., 1969

Species, Strain, Sex: mice, (C57BL/6 x C3H/KR)F_1, male

Body Weight: 0.36 kg (measured)

Length of Exposure (l_e) = 574 days

Length of Experiment (L_e) = 574 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: liver/hepatoma

Route, Vehicle: oral, by gavage in 0.5% gelatin for 21 days, then in diet for 553 days.

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	5/90
215 mg/kg/day x 21 days, 603 ppm in diet x 553 days	83.4	7/17

Human $q_1^* = 1.264 \times 10^{-1}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 7.91×10^{-5} mg/kg/day = 5.54×10^{-3} mg/day for 70 kg man

APPENDIX D

Cancer Data Sheet for Derivation of q_1^*

Compound: Chlorobenzilate

Reference: NCI, 1978

Species, Strain, Sex: Mice, $B6C3F_1$, male

Body Weight: 0.03kg low-dose, 0.025 kg high-dose (measured)

Length of Exposure (l_e) = 546 days

Length of Experiment (L_e) = 630 days

Lifespan of Animal (L) = days

Tumor Site and Type: hepatocellular carcinoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	4/19
4231 ppm for 546 days	476.7	32/48
7846 ppm for 546 days	884.0	22/45†

†This response was dropped because a chi-square test (45 FR 79318) indicated a poor fit to the multistage model.

Human $q_1^* = 5.51 \times 10^{-2}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 1.81×10^{-4} mg/kg/day = 1.27×10^{-2} mg/day for 70 kg man

APPENDIX E

Cancer Data Sheet for Derivation of q_1^*

Compound: Chlorobenzilate

Reference: NCI, 1978

Species, Strain, Sex: Mice, $B6CBF_1$, female

Body Weight: 0.02* kg low-dose, 0.023 kg high-dose

Length of Exposure (l_e) = 546 days

Length of Experiment (L_e) = 637 days

Lifespan of Animal (L) = 730 days

Tumor Site and Type: hepatocellular carcinoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	0/20
3200 ppm for 546 days	356.6	11/49
5908 ppm for 546 days	658.3	13/50

Human $q_1^* = 1.69 \times 10^{-2}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 6.17×10^{-4} mg/kg/day = 4.32×10^{-2} mg/day for 70 kg man